CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 83965

BIOEQUIVALENCE REVIEW(S)

Hydrochlorothiazide
50 mg Tablet
ANDA 83-965

Camall Company
Detroit, Michigan
AF #13-313
Submission Dated:
July 24, 1974

REVIEW OF A BIOAVAILABILITY PROTOCOL

1. This submission is a protocol for a bioavailability study to compare hydrochlorothiazide, 50 mg tablet (Camall Company) to the reference drug, Hydro-Diuril, 50 mg tablet (Merck, Sharp and Dohme).

2. The study is to be conducted by

3. The principal investigator will be Medical Director of His curriculum vitae has been submitted.

4. Male subjects selected for this study will be between the ages of 21 and 50 years. Weight range of the subjects will be within 10% of their ideal weight (in accordance with the Metropolitan Life Insurance Company Bulletin #40, Nov-Dec 1959).

5. Twenty normal healthy male adult volunteers will be chosen. Each subject will be free of significant gastrointestinal, renal or hepatic disease. In addition, subjects with a history of chronic alcohol consumption will not be eligible. Reference is made to the above in paragraph 8 under "COMMENTS".

6. A signed consent form will be obtained from each subject. These consent forms will describe the possible adverse reactions to the drug.

7. Laboratory tests will include CBC, BUN, FBS (fasting blood sugar), SGOT, alkaline phosphatase, serum bilirubin, differential white counts, and urinalysis with microscopic examination.

8. All subjects will abstain from any drug medication at least 7 days prior to the study and from any alcohol at least 72 hours before drug administration. No coffee will be permitted during both test days.

9. Only non-institutionalized subject volunteers will be used in this study.

10. Each drug will be assayed for content uniformity.

11. The subjects will be divided into two groups of 10 each. On the first test day, each subject will drink 8 ounces of water, 1 hour prior to administration of the drug. The subjects will ingest a single 50 mg tablet of the test or reference drug with 6-8 ounces of water on a twelve hour fasting stomach.

The second test day differs from the first, as the protocol states 6-8 ounces of water will be taken one hour prior to dosage time vs 8 ounces originally. This is noted in paragraph 5 under "COMMENTS".

12. Crossover interval will be one week. No food will be taken until 4 hours post dosage.

13. Urine specimens will be collected in the following fractions: 0-1, 1-2, 2-3, 3-4, 4-8, 8-12, and 12-24 hours. Additional collection times omitted appear in paragraph 6 under "COMMENTS".

Eight ounces of water will be given to the subjects at the time of each urine collection.

14. Each urine specimen will be measured for volume and pH.

15. The investigators will measure the amount of unchanged hydrochlorothiazide in the urine by the methods of Sheppard, Mowles and Plummer, Determination of Hydrochlorothiazide in Urine (J.A. Pharm. Assoc., Scientific Edition, Nov 1960).

16. The specificity, sensitivity, and linearity, to measure the drug at levels expected in the clinical specimens, will be submitted to validate the methodology.

17. All data, including recovery data, statistical curves, etc., are to be submitted with the report.

18. An ANOVAR will be done for the rate and amount of drug excretion for each sample collection period and for the cumulative 24 hour excretion.

19. Subjects will be monitored during the study day for adverse reactions. Any side effects will be reported.

COMMENTS:

1. Each subjects will be given a general physical examination fncluding history.

2. Each drug should be assayed for potency. In addition, dissolution studies should be conducted.

3. Tea and carbonated beverages are to be prohibited during the test days.

4. The amount of water intake prior to dosage for both test days should be the same.

5. The -1 to 0, 4-6, and 6-8 hour urine collection times which were omitted should be included.

6. The lot number's and the size of the production test batch should be remitted.

7. Each subject should be free of significant gastrointestinal, renal, and hepatic disease.

8. Each subject is to be informed that he is entirely free to withdraw from participation in the study at any time. Provision should be made for more than 20 volunteers to anticipate subject withdrawal.

RECOMMENDATION:

The company should be informed of COMMENTS 1 through 9. The protocol should be rewritten to include all the above comments. Approval of the protocol is recommended provided that comments 1 through 9 are adequately incorporated.

/S/

Katherine Apone
Clinical Research Branch

Hydrochlorothiazide
50 mg Tablets
ANDA 83-965

Camall Company
Submission Dated:
February 21, 1977

REVIEW OF A BIOAVAILABILITY STUDY

This study compared the urinary excretion of hydrochlorothiazide in 22 normal fasted subjects following administration of 50 mg of the Camall product or Hydrodiuril (MSD). The clinical part of the study was done by and the assays were done by The drug was given with eight ounces of water. Urine was collected at 0, 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-12, and 12-24 hour intervals after dosing. The crossover was done after a washout period of one week. The assay was the spectrophotometric method of Shepphard et. al. The raw data, standard curves, etc. were included in the submission.

The total average cumulative excretion for the 24 hour collection period was 26.75 mg for the Camall product and 27.91 mg for the MSD product. The rate of excretion was similar for each product and reached a peak in about three hours. The data was presented as rate per collection time and not as rate per hour. The area under the curve, therefore, is incorrect unless it is calculated from the rate per hour. The maximum rate per hour averaged 4.84 mg/hr for the Camall product and 5.38 mg/hr for the MSD product.

Dissolution was submitted using the method described in the USP XIX, page 651, in acid at 150 rpm. The average of six tablets gave 98.7% in 10 minutes for the Camall product and for the MSD product the average was 75.6% in 10 minutes, 88.1% in 20 minutes, and 92.0% in 30 minutes.

RECOMMENDATION:

The data shows that the Camall hydrochlorothiazide 50 mg tablet is bioequivalent to the MSD product and approval of the bioavailability requirement is recommended.

The dissolution specifications in the USP are being revised and the company will be requested to repeat the dissolution studies at 100 rpm in water using the rotating basket.

/S/

Harold R. Murdock, Ph.D.
Biopharmaceutics Review Branch